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Comparison of GnRH Agonist Long and Antagonist Protocols in the Same Normoresponder Patient Undergoing Assisted Reproductive Treatment

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ABSTRACT

Objective: Antagonists (ANT) are suspected to yield lower pregnancy rates compared to agonist (AL) protocols. The aim of the present study was to assess cycle characteristics and outcomes of a group of normoresponder women (NR) who had undergone controlled ovarian hyperstimulation with both ANT and AL protocols for assisted reproductive treatment (ART).

Materials and Methods: A retrospective comparative study was performed involving 50 NR patients. All the patients had been administered either an AL or ANT protocol at the initial attempt. Since a pregnancy could not be achieved or a pathological one was terminated, all the patients underwent a new cycle 3-6 months after the previous one, where the other protocol, unused in the first trial was employed. Stimulation characteristics and outcome of both protocols were compared in each patient.

Results: Stimulation duration was shorter (9.6 vs. 10.9 days; p<0.0001), peak E2 level was lower (2527 vs. 3042 pg/ml; p=0.028) and implantation rate was higher (17.3 vs. 9.7%; p=0.049) in ANT cycles compared to AL ones.

Conclusion: Antagonist protocol was observed to be as efficacious as agonist long one for superovulation of NR patients. Further studies are needed to support our belief that antagonists might be easily considered as the first choice in NR women undergoing ART.

Key words: *GnRH agonist, GnRH antagonist, normoresponders, assisted reproductive treatment (ART)*

ÖZET

Yardımla Üreme Tedavisi Uygulanan Normal Cevaplı Kadınlarda GnRH Agonist Uzun ve Antagonist Protokollerinin Karşılaştırılması

Amaç: Antagonist sikluslarında agonistlere göre daha düşük gebelik sonuçlarının elde edildiği öne sürülmektedir. Bu çalışma ile hem antagonist hem de agonist protokolü ile tedavisi olan bir grup normal cevaplı kadında bu iki protokolün siklus karakteristiklerinin ve tedavi sonuçlarının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Toplam 50 normal cevaplı kadında retrospektif karşılaştırmalı bir çalışma yapılmıştır. İlk uygulamada agonist uzun ya da antagonist protokolü ile tedavi yapılan bu 50 kadında gebelik elde edilemediğinde ya da patolojik bir gebelik termine edildiğinden 3-6 aylık bir dönemden sonra tekrar tedavi yapılmış ve ilk siklusta antagonist protokolü verilenlere agonist uzun, agonist uzun verilenlere ise antagonist protokolü verilmiştir. Aynı hastada her iki protokolün siklus karakteristikleri ve tedavi sonuçları karşılaştırılmıştır.

Bulgular: Antagonist protokolünde agonist uzun protokolüne göre siklus süresi daha kısa (9.6 ve 10.9 gün; p<0.0001), maksimum serum E2 düzeyi daha düşük (2527 ve 3042 pg/ml; p=0.028) ve implantasyon oranı daha yüksek (%17.3 ve %9.7; p=0.049) bulunmuştur.

Sonuç: Antagonist protokolü normal cevaplı kadınların yardımla üreme tedavileri için yapılan kontrollü over stimülasyonunda agonist uzun protokolü kadar etkindir. Yardımla üreme tedavisine alınan normal cevaplı olacağı düşünülen kadınların tedavisinde ilk seçenek olarak antagonistlerin kullanımı ileri çalışmalarla değerlendirilmelidir.

Anahtar Sözcükler: *GnRH agonist, GnRH antagonist, normal over cevabı, yardımla üreme tedavisi*

In vitro fertilization (IVF) treatment involves GnRH analogues for the prevention of premature LH surge. GnRH agonist use with the long protocol in IVF is considered the gold standard of ovarian stimulation and it is the result of more than 15 years experience (1). The GnRH agonist long protocol, starting in the midluteal phase of the preceding cycle, typically involves about three weeks of GnRH analogue treatment per cycle. In contrast, GnRH antagonists suppress premature LH surge during ovarian stimulation (2). They are administered between days 5-7 of stimulation when the risk of premature LH surge is most probable, therefore antagonist use lasts about 5-6 days per cycle. Treatment cycle is significantly shorter with GnRH antagonists than with GnRH agonist long protocol (3).

Although various studies have reported similar pregnancy rates, a meta-analysis indicated 5% less clinical pregnancies in the antagonist cycles compared with agonist long ones (4). These initial results together with the results of

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national large database evaluations cause clinicians not to choose GnRH antagonists at the first attempt (5). Moreover, GnRH antagonists were observed to be mainly used in older patients or those in whom previous cycles had been unsuccessful (5). However, sub-analysis of patients with equal demographic and clinical features showed similar pregnancy rates in GnRH antagonist cycles compared to agonist ones (6).

The aim of our study is to investigate whether antagonist protocol is as efficacious as agonist long one in ovarian stimulation for assisted reproductive treatment (ART) in women with normal ovarian response. In this study, we compared the stimulation characteristics and the treatment outcome in 50 women with normal ovarian response who underwent two ART cycles, one with GnRH agonist long and the other with antagonist protocol within a one-year period. Therefore, we evaluated the two most commonly used protocols, GnRH agonist long and antagonist protocols, in the same normoresponder patient cohort using their own historical controls to determine whether there was a difference between the two protocols as regards cycle parameters and outcome.

MATERIALS AND METHODS

In order to compare GnRH agonist long and antagonist protocols in the same normoresponder patient undergoing ART, the patient files were retrospectively reviewed to reveal the women with two ART cycles performed at our unit within one year period, one with the agonist long and the other with the antagonist protocol. A total of 50 patients with a mean age of 31 years who were treated at our IVF unit between May 2003 and June 2004 were included in the study. All 50 women had normal ovarian reserve at the initial evaluation and gave normal ovarian response with both stimulation protocols. Normal ovarian response was defined as the retrieval of five or more oocytes. Patients with PCOS, FSH >12 IU/l, autoimmune disorders, uterine pathology were excluded from the study. Informed consent was obtained from all of the patients. As this was a retrospective review of patient files, ethics committee approval was not required.

All the patients included had undergone COH with either a GnRH agonist long or antagonist protocol at the initial attempt. Since a pregnancy could not be achieved or a pathological one was terminated, all the patients underwent a new cycle 3-6 months after the previous one, where the other protocol, unused in the first trial was employed as the second treatment protocol: GnRH antagonist protocol instead of GnRH agonist long protocol or vice versa. Therefore in this study, each patient was compared with her own previous cycle. In our center, we usually use agonist long or antagonist protocol in normoresponder women. The determinants of the protocol to be used for the first attempt are not defined and mostly depends on the preference of the physician.

In agonist long protocol, GnRH agonist leuprolide acetate (Lucrin®, Abbott, France) was initiated at 0.5 mg/day dose on the 21st day of the preceding cycle and gonadotropins were added on the third day of menses. Gonadotropins (recombinant FSH and/or human menopausal gonadotropin [hMG]) were started at a dose of 150-300 IU daily according to age, antral follicle count, BMI and previous cycles, if present. In GnRH antagonist protocol, gonadotropins were initiated on the second day of menses at the same doses mentioned above and when the leading follicle reached a diameter of 14 mm, GnRH antagonist (Cetrotide®, Serono, Switzerland or Orgalutran®, Organon, Netherlands) was administered 0.25 mg daily until HCG injection. The gonadotropin doses were adjusted according to the serial sonographic follicular sizes and serum estradiol (E2) measurements. When the leading follicle reached 20 mm in diameter, human chorionic gonadotropin (HCG; Pregnyl®, Organon, Netherlands) 10.000 IU was administered. Ooocyte pick-up was arranged 36 hours after HCG injection. All the patients received luteal phase support with progesterone in oil 75 mg daily starting from the day after oocyte retrieval. If pregnancy was achieved, micronized progesterone vaginal suppositories (Progestan®, Kocak, Turkey) 600 mg daily were continued until 12 weeks' gestation. Embryo transfer was performed on days three to five under ultrasound guidance. A serum beta HCG measurement was ordered 12 days after embryo transfer procedure. In case of positive pregnancy test result, an ultrasound was performed three weeks afterwards.

Cycle characteristics and the outcome of the two stimulation protocols in each patient were compared. The primary aim of the present study was to compare the implantation, pregnancy and early pregnancy loss rates between the agonist long and antagonist cycles in the same patient. Secondary aims were to evaluate and compare the stimulation characteristics and the outcome of ART cycles in terms of total gonadotropins used, stimulation duration, serum E2 levels and endometrial thickness on the day of HCG administration, numbers of total and mature oocytes retrieved, fertilization rate and embryo quality. A serum β-HCG value >10 IU/l indicated pregnancy. Early pregnancy loss was considered when the pregnancy did not continue beyond 12th gestational week after the positive pregnancy test result. Implantation rate was defined as the ratio of the number of gestational sacs per number of embryos transferred.

Categorical data were expressed as percentage and number, and numerical data as mean and standard deviation. Statistically significant differences were determined using the Student's *t*-test, Chi-square test and Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 50 patients who underwent ART with both GnRH agonist long and antagonist protocols within a one-year period were evaluated regarding cycle characteristics and treatment outcome. The causes of infertility were male factor (62%), tubal factor (14%), unexplained infertility (22%) and endometriosis (2%). The mean ages for women were 31.4 years vs. 31.8 years in agonist long and antagonist cycles. In 33 of those 50 women (66%), GnRH agonist long protocol was administered at the first treatment attempt and in the remaining 17 women (34%), GnRH antagonist protocol was the preferred stimulation protocol in the first trial.

Out of 50 GnRH agonist long cycles, 16 (32%) and out of 50 GnRH antagonist cycles 26 (52%) resulted in pregnancy ($p>0.05$, Figure 1). Implantation rate was found to be higher, although at borderline significance, in antagonist cycles (17.3% vs. 9.7%, respectively; $p=0.049$) than in agonist long ones (Figure 1). Early pregnancy loss rate was

found to be similar in agonist long and antagonist cycles (38% vs. 19%; p>0.05; Figure 1).

Duration of gonadotropin stimulation was longer (10.9±1.6 days vs. 9.6±1.2 days; p<0.0001) and serum E2 level on the day of HCG administration was higher (3042±1361 pg/ml vs. 2527±897 pg/ml; p=0.028) in agonist long protocol compared to antagonist one. No statistically significant difference was found between the two stimulation protocols for the amounts of gonadotropins used, total and mature oocytes retrieved, endometrial thickness on the day of HCG administration, fertilization rate, number of grade I embryos transferred, embryo quality and the day of embryo transfer (Table 1).

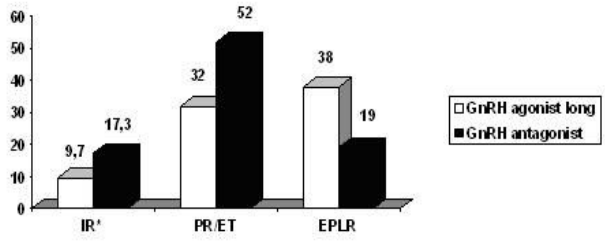

Figure 1. Implantation rate (IR), pregnancy rate per embryo transfer (PR/ET) and early pregnancy loss rate (EPLR) in 50 normoresponder women who underwent assisted reproductive treatment with both GnRH agonist long and antagonist protocols within a one-year period. (*p=0.049)

Table 1. Cycle characteristics and treatment outcomes of 50 patients who underwent ovarian stimulation for ART with both agonist long and antagonist protocols within a one-year period.

	Agonist long protocol	Antagonist protocol	P
1st attempt, %	66	34	
Age (years)	31.4±4.0	31.8±4.1	
Infertility duration (years)	7.1±4.4	7.6±4.5	
BMI (kg/m2)	24.2±2.9	24.6±3.3	
Total gonadotropin used (IU)	2875±1267	2514±972	NS
Stimulation duration (days)	**10.9±1.6**	**9.6±1.2**	**<0.0001**
HCG E2 (pg/ml)	**3042±1361**	**2527±897**	**=0.028**
HCG endometrium (mm)	11.6±2.3	11.3±1.9	NS
Total oocyte, n	16.1±6.5	15.6±6.3	NS
MII oocyte, n	11.7±5.2	11.7±5.3	NS
MII oocyte, %	72	74	NS
Fertilization, %	77	82	NS
Grade I embryos transferred, n	2.7±1.5	2.9±1.4	NS
8-cell emb.no/total emb.no. on day 3, %	30	32	NS
ET day	3.5±0.8	3.5±0.7	NS
Day 3 ET's, %	62	64	NS
Day 5 ET's, %	20	12	NS
Implantation, %	**9.7**	**17.3**	**=0.049**
Bhcg (+) pregnancy/embryo transfer, % (n)	32 (16/50)	52 (26/50)	NS
Early pregnancy loss, % (n)	38 (6/16)	19 (5/26)	NS

Values are means± SD or percentages, NS= not significant; p>0.05
(BMI, body mass index; HCG, human chorionic gonadotropin; MII, metaphase II; ET, embryo transfer)

DISCUSSION

There is a debate regarding the best stimulation protocol which should be the first choice in a normoresponder woman. Given the high discontinuation rates when pregnancy has not been achieved (7, 8), it is essential to determine the best possible stimulation protocol in normoresponder patients. We aimed to determine whether GnRH agonist long and antagonist protocols yielded significant differences in cycle parameters and treatment outcome when performed in the same normoresponder woman in a one-year period. The results of the present study showed shorter stimulation duration, lower peak E2 levels and a higher implantation rate in antagonist cycles compared to agonist long ones.

GnRH agonists have been introduced in the mid 1980s in order to prevent LH surge in IVF cycles (9, 10). GnRH agonist long protocol has a widespread popularity and is still the predominantly used method of ovarian stimulation in IVF. One decade later, GnRH antagonists have been introduced in the mid 1990s for the suppression of endogenous LH increase in ovarian stimulation (2,11).

Although antagonist protocol has been used mainly in poor responder and older women, it has been proposed as a patient friendly treatment regime which might be the most probable stimulation protocol to improve patient experience (12).

Several investigators have indicated lower pregnancy rates in antagonist cycles compared to agonist ones (13,14). However, the problem with GnRH antagonist protocol is its use mainly in poor responder and older patient groups and the fact that it is not the first choice of clinicians. Prior randomized and nonrandomized studies have revealed various results. Therefore, well-designed studies are needed to establish the efficacy of antagonists separately in poor responder, normoresponder and high responder-PCOS patient groups.

The preferred ovarian stimulation protocol for normoresponder women varies according to the center. While choosing the right protocol, consideration should be given to treatment cost, ease of use, treatment risk and psychological distress (12). GnRH agonist long protocol is still the most commonly used one for ART cycles worldwide and antagonist protocol is not preferred in the first attempt in normoresponder women which might be due to its initial use in poor responder and older patient groups. However, in recent years antagonist protocol has gained popularity and especially in PCOS cases it is suggested as the first choice in some centers in order to prevent ovarian hyperstimulation syndrome (15). Similarly in a recent prospective study, flexible GnRH antagonist protocol was found to be associated with a similar ongoing pregnancy rate compared with GnRH agonist in PCOS patients undergoing IVF (16).

To the best of our knowledge, most of the studies present in the literature regarding antagonist use have been performed in poor responder and PCOS patients and also in a general IVF patient population. Studies regarding antagonist use in normoresponder women are scarce and revealed contradictory results. Antagonists are suspected to yield lower pregnancy rates compared with the agonist long protocol, therefore there is still controversy on the use of antagonist protocol as the first choice in normoresponder women. Orvieto et al. (17) suggested that the GnRH agonist long protocol should be the protocol of choice in young patients in their first three IVF cycle attempts. Another study in good prognosis women (<35 years, IVF range one or two) revealed significantly lower pregnancy rates in antagonist cycles compared to agonist long ones (18). However, a recent study comparing the GnRH agonist long and the antagonist protocols in young women (<35 years) with tubal factor infertility reported similar pregnancy rates supporting the hypothesis that both regimes lead to equal results (6). Furthermore, it has been shown that antagonist use in ovarian stimulation for ART is at least as effective as the GnRH agonist long protocol in patients with normal ovarian response and antagonists even allow a higher flexibility in the treatment (19, 20). Similarly, the results of the current study revealed that the GnRH antagonist and agonist long protocols provided comparable outcomes in the same patient undergoing ART and even shorter stimulation duration and higher implantation with antagonists. We concluded that GnRH antagonist protocol might be considered as comparable and even better compared with agonist long protocol in a normoresponder woman. Accordingly, we suggest that in patients with the failure of the either protocol in the first attempt, the other one might be considered safely for the next treatment cycle instead of giving the same protocol again. Moreover, in a recent prospective study, no significant difference was found between antagonist and agonist groups in terms of pregnancy and delivery complications, neonatal outcome and risk of major malformations (21).

Optimal comparisons between GnRH agonist long and antagonist protocols are still lacking. As the implantation rate was suggested to be adversely affected in antagonist cycles, we performed such a study where each patient was compared with her own previous cycle. In every patient a GnRH antagonist protocol was used in the new cycle instead of a GnRH agonist long protocol used in the previous cycle or vice versa. The probability of reduced ovarian response over time might be considered as a bias for this study. However, the time period between the two treatment cycles were 3-6 months in this normoresponder patient group and both cycles were performed within a one-year period.

In conclusion, our data comparing the most commonly used two protocols, GnRH agonist long and antagonist protocols in the same normoresponder patient cohort show a favourable outcome with antagonists. The data revealed better results in terms of stimulation duration, peak estradiol levels and implantation rate in antagonist cycles compared to agonist long ones in normoresponder patients. Further studies are needed to support our belief that a GnRH antagonist regimen might be easily considered as the first choice in normoresponder women undergoing ART.

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